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Ultrasonic Analysis of Plaque Characteristics and Intimal-medial Thickness in Radiation-induced Atherosclerotic Carotid Arteries

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Objectives: *to investigate the effect of external irradiation on the morphology of atherosclerotic plaques and the intimal-medial thickness of the carotid artery.*
Methods: *a group of 46 patients (16 symptomatic) who had received external irradiation to the head and neck area more than five years previously and developed carotid stenosis exceeding 50%, were evaluated by duplex ultrasound. The carotid artery lumen, intimal-medial complex, and the plaque echogenicity was determined using computer digital image processing methods. Forty-six age and sex matched patients with similar degrees of non-radiation associated carotid stenosis were used as controls.*
Results: *irradiated stenotic carotid arteries had a greater intimal-medial thickness (0.96 mm vs 0.80 mm, $p = 0.008$) and a narrower lumen (5.5 mm vs 6.6 mm, $p < 0.001$) than the controls. The carotid plaque characteristics (gray-scale median (GSM) and heterogeneity) of the irradiated and control groups did not differ significantly. Symptomatic patients who had received external radiotherapy to the head and neck have a more echolucent plaque (mean GSM of 98) than their asymptomatic counterparts (mean GSM 114, $p = 0.03$). Intimal-medial thickness and carotid lumen was not related to the occurrence of symptoms.*
Conclusions: *external irradiation to the head and neck area leads to significantly increased thickness of the carotid wall and a corresponding narrowing of the lumen. There seems to be no difference in the plaque characteristics between irradiation-induced and spontaneous carotid atherosclerosis.*

Key Words: Carotid artery; Radiation effects; Ultrasonography.

Introduction

External irradiation produces damage to the carotid arteries via endothelial damage, periadventitial fibrosis, and obliteration of the vasa vasorum.[1] It has been shown that patients who had received external irradiation to the head and neck area for malignancy have a higher incidence of significant extracranial carotid artery stenosis, particularly years after irradiation injury.[2–4]

Although the NIH Asymptomatic carotid stenosis trial has confirmed the efficacy of carotid endarterectomy on patients with carotid stenosis of >60%, it is generally accepted that a perioperative stroke risk of less than 3% is required for the procedure to be beneficial.[5] Carotid surgery on a patient with previous neck irradiation is hazardous due to adhesions in an irradiated field and obliteration of anatomical planes, and incurs a higher morbidity.[6] The natural history of asymptomatic carotid stenosis in these patients with head and neck malignancies is not known, and treatment recommendations further made uncertain by the patients' often limited life expectancy. Nevertheless with modern radiotherapy and surgery long term survivors of head and neck cancer do exist, who may benefit from stroke prevention procedures.

Carotid plaque morphology has been shown to be an important factor causing stroke.[7,8] It has been assumed that the carotid lesion in an irradiated artery arises from an accelerated atherosclerotic process, and the patient's subsequent risk of stroke would be similar to those who did not receive radiation but with an equivalent degree of luminal stenosis. However it is not known whether plaques in irradiated arteries have a composition similar to non-irradiated, spontaneous atherosclerotic plaques, and behave likewise. The relative contribution of wall fibrosis and intimal-medial thickness and its effect on luminal diameters are also unclear. Modern high resolution

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ultrasonography enables further risk stratification based on analysis of plaque structure, and may provide the answer to these questions.

Carotid stenosis develops consistently only a few years after irradiation, and the efficacy of intervention early in asymptomatic post-irradiation patients is not established owing to an uncertain long-term prognosis. Therefore the group of individuals who would benefit most from carotid plaque studies is those who have a long history of neck irradiation and with an established degree of stenosis in their arteries. This study aims to examine, by a cross sectional analysis, the ultrasound characteristics of carotid plaques as well as the intimal-medial thickness (IMT) in a group of patients who has received prior long term external irradiation to the head and neck area and who had a carotid stenosis exceeding 50%, compared to non-irradiated controls.

Patients and Methods

Patients and disease characteristics

Since 1998, an ultrasound screening program for carotid stenosis was offered to all patients from the Department of Surgery, University of Hong Kong Medical Centre who had received radiotherapy to the head and neck area for malignancies. Patients were selected for this study if they had (1) evidence of a $>50\%$ stenosis in the common or internal carotid arteries on duplex ultrasound and (2) survived more than five years since radiotherapy. Those with prior carotid artery surgery or angioplasty were excluded. The study population consisted of 46 patients who met the above criteria, sixteen of whom gave a history of cerebrovascular symptoms prior to the carotid duplex ultrasound examination (10 established stroke, six transient ischemic attacks), with a median of nine months before the duplex scan (range 1–26 months).

Another group of 46 patients who did not receive radiotherapy to the head and neck, but had a $>50\%$ carotid stenosis on duplex ultrasound was randomly selected as controls from the laboratory database. The control group of patients was matched for sex, age, percent carotid stenosis, and the presence and absence of symptoms with the radiotherapy group.

The patients who had received radiotherapy (RT group) and the control group each consisted of 42 men and four women, with a mean age of 64.0 years for the RT group and 65.8 years for the controls (range: 40–85 years). The primary malignancy of the patients included nasopharyngeal carcinoma ($n=19$), carcinoma of the larynx ($n=20$) carcinoma of the oropharynx ($n=3$) and carcinoma of the parotid ($n=2$) and oral cavity ($n=2$). All patients were given standard regimens of bilateral cervical irradiation of 60 Gray to the primary region, and 50 to 60 Gray to the neck depending on regional lymph node status; except the four patients with parotid and oral cavity cancer who received 50 Gray to the unilateral neck. The median interval from external irradiation to ultrasound examination for the RT group was 136 months (range 64–336 months). Eighteen patients had prior resection for their primary tumor, including 11 laryngectomy. Only six patients had an additional radical neck dissection.

Sixteen patients from each group had reported previous symptoms corresponding to the side of the carotid stenosis. Since the groups are selected to be stenosis-matched, each has a mean ICA/CCA stenosis of 75% (50–99%).

Ultrasound examination

All patients and control subjects underwent a carotid artery color flow doppler examination in our Vascular Laboratory by one single Registered Vascular Technologist using the Acuson 128XP-10 scanner (Acuson Corporation, Mountain View, CA, U.S.A.) and a 5 Mz probe (L5). The percent stenosis of the common carotid (CCA) and internal carotid (ICA) arteries were recorded using standard criteria based on peak systolic velocity and end diastolic velocity as well as ICA/CCA ratios. The carotid duplex examination has been validated by comparison with conventional angiography to have a sensitivity of 94% and specificity of 86% for the detection of $>70\%$ internal carotid artery stenosis. To maintain mutually independent status on statistic analysis, the artery from the side with dominant stenosis or relevant symptomatic artery ipsilateral to cerebral ischemic symptoms was selected.

Carotid plaque ultrasonic morphology

Carotid plaque echogenicity was measured by a method described previously and modified for our laboratory scanner.[8,9] An optimal image of the relevant carotid plaque was visualised on duplex with a standardised B-mode setting with an echo dynamic range of 48 ± 5 dB and linear postprocessing, with the dynamic range equally divided throughout the gray levels. The time gain compensation was set at vertical so that the entire image can be of similar brightness for all scans. The video images were stored on super VHS tape, and subsequently captured using

a computer graphics capture board (Targa 1000 Pro, Truevision Inc., Santa Clara, CA, U.S.A.) on a Windows NT 4.0 workstation using DVR32 version 3.1 software, digitised at a resolution of 720 × 576 pixels, and stored in CD media. The digitised images were converted to gray-scale and the level normalised with a 256 gray-scale range with respect to blood = 0–5, maximal white according to a linear reference scale = 256. This would give gray-scale value of the adventitia of about 230. The plaque outline is mapped manually using a commercial image processing software (Adobe Photoshop v5.0) and the gray-scale histogram was calculated. Data regarding the gray-scale median (GSM), and its standard deviation (homogenicity) was obtained from the histogram.

Intimal-medial thickness measurement

A longitudinal view of the common and internal carotid artery was obtained separately using the duplex scanner and stored and captured as described above. The intimal-medial thickness (IMT) was determined by the far wall measurements taken at the common carotid artery away from the atherosclerotic plaque and averaged over three readings on a magnified image.[10] The same technician blinded to the irradiation status was responsible for analysis of all images. The maximal intimal-medial thickness of the far wall and the minimal vessel lumen of the common and the internal carotid arteries were determined.

Statistical analysis

The IMT, GSM and GSM standard deviation, degree of stenosis, and the common and internal carotid artery lumen values were normally distributed and were compared between the irradiated and control groups, and also between symptomatic and asymptomatic patients using the Student's *t*-test, with a statistical significance chosen at $p < 0.05$. All statistical tests were performed using the Statistical Package of Social Sciences version 9.0 (SPSS Inc., Chicago, IL, U.S.A.).

Results

The ultrasonic plaque and wall parameters were listed in Table 1.

Intimal-medial thickness and carotid lumen

The mean carotid IMT of the RT group was significantly greater than the controls (0.96 mm vs 0.80 mm, $p = 0.008$). The common carotid artery lumen was correspondingly narrowed for the RT patients (mean 5.5 mm) compared with the controls (mean 6.6 mm, $p < 0.001$). The internal carotid artery lumen did not differ significantly between the two groups.

Ultrasonic plaque morphology

The ultrasonic plaque characteristics, including GSM, heterogeneity, and standard deviation between the RT and the control group did not show a significant difference (Table 1).

Plaque GSM and symptoms

For the RT group, the symptomatic patients have a significantly more echolucent plaque (mean GSM of 98) than the asymptomatic group (mean GSM 114, $p = 0.03$) (Table 2). They also exhibited a higher degree of luminal stenosis (91% vs 67%). In the control group, symptomatic patients also have a more echolucent plaque (mean GSM of 104 vs 107, $p = 0.07$), although the difference is not statistically significant. IMT and

Table 1. Plaque characteristics and wall thickness in patients with irradiated and non-irradiated stenotic carotid arteries.

Parameter	Radiotherapy group ($n = 46$)	Control group ($n = 46$)	*p* value
IMT (mm)	0.96 ± 0.34 (0.48–2.33)	0.80 ± 0.19 (0.47–1.36)	0.008
GSM (of 256)	109 ± 27 (58–172)	106 ± 25 (65–160)	0.62
GSM-SD	34 ± 8 (20–55)	35 ± 11 (5–64)	0.73
Stenosis (%)	76 ± 19 (60–100)	76 ± 19 (60–100)	1.0
CCA lumen (mm)	5.5 ± 1.1 (2.9–7.6)	6.6 ± 1.2 (4.0–9.5)	< 0.001
ICA lumen (mm)	4.3 ± 0.8 (3.0–5.9)	4.4 ± 0.7 (3.1–5.7)	0.56

Values given are mean ± standard deviation (range).
IMT = Common carotid intimal-medial thickness; GSM = Plaque grey-scale median; GSM-SD = Standard deviation of plaque grey-scale median; CCA = Common carotid artery; ICA = Internal carotid artery.

Table 2. Plaque characteristics and wall thickness in patients with irradiated and stenotic carotid arteries stratified by symptoms.

Parameter	Symptomatic group ($n=16$)	Asymptomatic group ($n=30$)	p value
IMT (mm)	0.92 ± 0.43 (0.48–2.33)	0.98 ± 0.29 (0.61–2.12)	0.62
GSM (of 256)	98 ± 18 (71–125)	114 ± 30 (58–172)	0.03
GSM-SD	33 ± 8 (20–52)	35 ± 9 (23–55)	0.33
Stenosis (%)	91 ± 8 (70–100)	67 ± 17 (60–100)	<0.001
CCA lumen (mm)	5.9 ± 1.3 (2.9–7.6)	5.3 ± 1.0 (3.8–7.3)	0.11
ICA lumen (mm)	4.4 ± 0.8 (3.1–5.8)	4.3 ± 0.7 (3.0–5.9)	0.50

Values given are mean ± standard deviation (range);
IMT = Common carotid intimal-medial thickness; GSM = Plaque grey-scale median; GSM-SD = Standard deviation of plaque grey-scale median; CCA = Common carotid artery; ICA = Internal carotid artery.

CCA/ICA lumen have no association with the occurrence of symptoms.

Discussion

External irradiation to the head and neck area is known to be complicated by accelerated atherosclerosis and stenosis of the common and internal carotid arteries, which often involve atypical sites and long segments. We have demonstrated previously that significant carotid stenosis of >70% occurred in 12% of 240 patients who had underwent external radiotherapy for head and neck malignancies.[4] Dubec *et al*. also reported that 38% of 45 patients with previous head and neck irradiation were found to have carotid stenosis of 50% or more.[2] Another group of investigators reported a 22% incidence of high grade stenosis, 80% of patients being symptomatic.[3] Although the association of external irradiation to the neck and subsequent carotid atherosclerosis is established, the morphological changes at the plaque and vessel wall level and their associated prognostic importance has not been previously investigated.

The mechanism of irradiation-associated carotid stenosis is believed to be a combination of direct vessel wall damage, with intimal proliferation followed by necrosis of the media, periadventitial fibrosis, and accelerated atherosclerosis from intimal thickening and medial hyperplasia. In arterioles, the effect of radiotherapy consists mainly of myointimal proliferation and macrophage infiltration with fibrinoid medial necrosis and replacement of the media with collagen. In medium sized arteries the lipid deposits and atheromas and fibrosis may be indistinguishable from spontaneous atherosclerosis.[1] Obliteration of the vasa vasorum is also postulated to be a key factor in inducing wall changes. It is not known whether these mechanisms would produce ischemic events at the intimal-medial level that will lead to modification of the plaque characteristics in a form different from non-irradiation induced atherosclerosis, or promote ulceration.

In addition to degree of stenosis, recent interest was focused on the histology and composition of the carotid plaque[11] and their relationship to the risk of stroke. In a qualitative ultrasound analysis of 223 subjects with carotid stenosis Mathiesen *et al*. showed that echolucent atherosclerotic plaques have a higher risk of ischemic cerebrovascular events.[7] In another prospective follow-up study, echolucent plaques in symptomatic patients with ≥50% carotid stenosis were found to have an three-fold increase in risk of future stroke compared to patients with echorich plaques.[12]

Modern high resolution duplex ultrasound allows carotid artery morphology to be studied in detail and may provide the answer to whether atherosclerotic plaques structure and carotid wall thickness in irradiated arteries are similar to those from arteries with spontaneous atherosclerosis. Nicolaides and his group pioneered a quantitative method of studying plaque morphology using a computer digitised image analysis. They have shown that hypoechoic plaques (with a low GSM) are more embologenic and are associated with hemispheric symptoms, particularly amaurosis fugax.[8] Hyperechoic plaques are fibrous and rich in collagen, while hypoechoic plaques contain lipids with little fibrous tissue, are less stable, and prone to intraplaque hemorrhage and embolism.

We have demonstrated on a cross section analysis that patients with carotid stenosis after irradiation exhibit a pattern of plaque morphology no different from age-matched controls. On the other hand within the confines of sample size, a low GSM score is associated with recent cerebrovascular symptoms, confirming that the relationship of plaque echolucency and cerebral events applies to irradiated carotid arteries as well.

Atherosclerotic plaques in irradiated arteries take time to develop.[4] We have chosen only arteries with

at least a 50% stenosis to obtain plaque areas large enough for an accurate image analysis. The majority of the patients in this study population were long-term survivors of their malignancy, and had an extended interval from their original radiation injury for stenotic plaques to develop. These are patients who would benefit most from carotid intervention with the aim of stroke prevention. We accept the disadvantage of a cross sectional study and the possibility of dynamic changes of atherosclerotic plaques, and did not include patients with early irradiation injuries where there may be acute vasculiitis and cellular infiltrates, subendothelial oedema, and underdeveloped plaques of questionable significance.

The method of measuring plaque GSM has been slightly modified from the original. We calibrated the maximal white level using an internal reference scale of 256 instead of using the adventitial value to maximise the resolution and dynamic range of the plaque image analysis. The GSM of the adventitia was consistently determined to be around 90% (or 230 of 256) of the maximal gray-scale using this method. Since we are not referring to absolute GSM values but rather compare the plaque echodensity between two populations, the choice of reference should not influence the results.

IMT, the combined thickness of the intima and media measured on duplex scan, is a good reflection of the intimal medial thickness on histological examination.[13] Recent evidence has shown that the common carotid IMT is associated with atherosclerosis and myocardial infarction and stroke.[14] In a prospective study involving 36 patients, Muzaffar showed that external irradiation significantly increases the carotid IMT during the first year after irradiation,[15] and the changes appeared to be progressive. The results of this study established that this thickening of IMT is persistent to more than ten years after irradiation, with a concomitant narrowing of the common and internal carotid artery lumen independent of the degree of carotid stenosis.

IMT measurement on ultrasonography cannot distinguish between intimal atherosclerosis and medial hypertrophy. It is possible that the intimal-medial thickening is a combined result of both fibrin accumulation in the medial and intimal layers, and their gradual replacement with collagen. The increase in IMT in patients with radiotherapy represents a reaction to an external injury and probably has no prognostic significance to cardiovascular events. Measurements of the luminal diameter of an ultrasonic image are also subject to variation as they may not always accurately reflect the smallest diameter of the carotid artery on longitudinal section. Nevertheless the thickening in IMT, supplemented by a finding of a narrower luminal diameter of the artery, may be important when considerations are given for choosing surgery or angioplasty in treating patients with irradiation-associated carotid stenosis.

Conclusion

Carotid plaques in irradiated patients do not differ from those arising from spontaneous atherosclerosis in the general population and probably should be considered in a similar context regarding prognosis. Irradiation to the neck produces a thickening of the intimal-media complex as well as narrowing of the carotid artery lumen which may have long-term effects in blood flow reduction and stroke. The clinical implications of these findings with regard to neurological events and treatment are unknown and need to be ascertained by further studies.

References

1 Fajardo LF. Is the pathology of radiation injury different in small vs large blood vessels? *Cardiovasc Radiat Med* 1999; **1**: 108–110.
2 Dubec JJ, Munk PL, Tsang V, Lee JM, Janzen DL, Buckley J, Seal M, Taylor D. Carotid artery stenosis in patients who have undergone radiation therapy for head and neck malignancy. *Br J Radiol* 1998; **71**: 872–875.
3 Carmody BJ, Arora S, Avena R, Curry KM, Simpkins J, Cosby K, Sidawy AN. Accelerated carotid artery disease after high-dose head and neck radiotherapy: is there a role for routine carotid duplex surveillance? *J Vasc Surg* 1999; **30**: 1045–1051.
4 Cheng SWK, Wu LLH, Ting ACW, Lau H, Lam LK, Wei WI. Irradiation-induced extracranial carotid stenosis in patients with head and neck malignancies. *Am J Surg* 1999; **178**: 323–328.
5 Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995; **273**: 1421–1428.
6 Rockman CB, Riles TS, Fisher FS, Adelman MA, Lamparello PJ. The surgical management of carotid artery stenosis in patients with previous neck irradiation. *Am J Surg* 1996; **172**: 191–195.
7 Mathiesen EB, Bonaa KH, Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis. The Tromso Study. *Circulation* 2001; **103**: 2171–2175.
8 Sabetai MM, Tegos TJ, Nicolaides AN, El-Atrozy TS, Dhanjil S, Griffin M, Belcaro G, Geroulakos G. Hemispheric symptoms and carotid plaque echomorphology. *J Vasc Surg* 2000; **31**: 39–49.
9 Elatrozy T, Nicolaides A, Tegos H, Zarka AZ, Griffin M, Sabetai M. The effect of B-mode ultrasonic image standardization on the echodensity of symptomatic and asymptomatic carotid bifurcation plaques. *Int Angiol* 1998; **17**: 179–186.
10 O'Leary DH, Polak JF, Wolfson Jr SK, Gene Bond M, Bommer W, Sheth S, Psaty BM, Shaarrett AR, Manolio TA. Use of sonography to evaluate carotid atherosclerosis in the elderly. The Cardiovascular Health Study. *Stroke* 1991; **22**: 1155–1163.
11 Carr SC, Cheanvechai V, Virmani R, Pearce WH. Histology and clinical significance of the carotid atherosclerotic plaque: implications for endovascular treatment. *J Endovasc Surg* 1997; **4**: 321–325.

12 Grønholdt MM, Nordestgaard BG, Schroeder TV, Vorstrup S, Sillesen H. Ultrasonic echolucent carotid plaques predict future strokes. *Circulation* 2001; **104**: 68–73.
13 Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation* 1986; **74**: 1399–1406.
14 O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med* 1999; **340**: 14–22.
15 Muzaffar K, Collins SL, Labropoulos N, Baker WH. A prospective study of the effects of irradiation on the carotid artery. *Laryngoscope* 2000; **110**: 1811–1814.

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